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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,011	06/19/2006	Beatrice Schaack	284025US0XPCT	8486
22850 7590 06/30/2009 OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER VIVLEMORE, TRACY ANN	
			ART UNIT 1635	PAPER NUMBER
			NOTIFICATION DATE 06/30/2009	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/563,011	<b>Applicant(s)</b> SCHAACK ET AL.	
	<b>Examiner</b> Tracy Vivlemore	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 April 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-15, 17-21, 24, 25 and 27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15, 17-21, 24, 25 and 27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                          | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

### ***Claim Rejections - 35 USC § 103***

Claims 1-15, 17-21, 24, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt (US 6,440,738, of record) in view of Bass (Nature 2001, of record) and Fosnaugh et al. (US 2003/014732, of record).

The claims are directed to double stranded complementary oligonucleotides of 17-21 nucleotides, or fragments 80% identical to them, that are targeted to human casein kinase 2. In specific embodiments, the oligonucleotide is targeted to SEQ ID NO: 26, the strands comprise 5' phosphate groups, have 3' overhangs of tt or aa, are 19-20 or 21-23 nucleotides in length, are present in expression cassettes, vectors or cells, or are formulated as mixtures of oligonucleotides, including a mixture of oligonucleotides targeted to three different subunits. In other embodiments, siRNAs are combined in compositions with chemotherapeutic or antiviral agents.

Wyatt teaches antisense oligonucleotides targeted to the  $\beta$ -subunit of human casein kinase 2 which is represented by SEQ ID NOs: 3 and 17. Wyatt teaches at column 2 that human casein kinase 2 expression is involved in several types of cancer and in viral replication. At columns 27-28 Wyatt teaches that pharmaceutical compositions of antisense oligonucleotides can be combined with either

chemotherapeutic or antiviral agents. In table 1, Wyatt teaches several antisense oligonucleotides, one of which, SEQ ID NO: 60, is targeted to a region sharing 16 nucleotides with the elected target region represented by SEQ ID NO: 26. Wyatt does not teach siRNAs targeted to the  $\beta$ -subunit of human casein kinase 2.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. Bass further teaches in the same column that the discovery of short interfering RNAs that are functional in mammalian cells will inspire further research studies aimed at optimizing the use of siRNAs, as well as at understanding why conventional RNAi using longer dsRNA works in eggs and embryos. Bass speculates that, based on the huge impact the RNAi technique has had in studies of non-mammalian systems, use of siRNA in mammalian cells could be just as far-reaching, with applications extending to functional genomics and therapeutics.

Fosnaugh et al. teach that siRNAs are made of a sense and antisense strand and are useful for a variety of therapeutic, diagnostic, agricultural, target validation, genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught in the

figures and at pages 3-8, including 5' phosphate groups at paragraph 46, 3' overhangs at paragraph 17 and lengths of siRNAs of 19-25 nucleotides at paragraph 33. Figure 4 teaches the specific embodiment of tt overhangs. Paragraph 25 teaches expression vectors and cells comprising siRNAs. Paragraphs 195-200 teach siRNA compositions comprising formulations that allow cellular penetration and targeting of specific tissues or organs. In example 3, Fosnaugh et al. teach production of pools of siRNAs. Fosnaugh et al. is considered to comprise a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs targeted to the  $\beta$  subunit of human casein kinase 2 and to produce these siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications as taught by Fosnaugh et al. One of ordinary skill in the art would have had a motivation to make siRNAs targeted to casein kinase 2 because Wyatt teaches the role of casein kinase 2 in cancers and viral replication and teaches that antisense oligonucleotides targeted to this gene are useful in inhibiting expression and because Bass teaches that inhibition of gene expression using siRNAs has the advantages of working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. One of ordinary skill in the art would have had a motivation to make these siRNAs with the features recited in the instant claims because Fosnaugh et al. explicitly teach the advantages of siRNAs having these characteristics. Because Wyatt teaches inhibition of casein kinase 2 by

making and testing a multitude of oligonucleotides targeted throughout the gene sequence and because Fosnaugh et al. provide a detailed teaching of how to make and use siRNAs to any known gene, one of ordinary skill in the art would recognize that targeting an siRNA to SEQ ID NO: 26 with the siRNA sequences in claims 6 and 8 to be a matter of design choice and routine optimization to find siRNAs having the best properties for a desired application. Based on the suggestion of Wyatt that inhibitors of casein kinase 2 be combined with additional chemotherapeutic or antiviral agents, one of ordinary skill in the art would also combine siRNAs targeted to casein kinase 2 with these agents and based on the teaching by Fosnaugh et al. that multiple siRNAs can be combined into one composition, one of ordinary skill in the art would recognize that siRNAs to different targets could also be combined. One of ordinary skill in the art would have had a reasonable expectation of success in producing human casein kinase 2 siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications because synthesis of nucleic acids containing modified nucleotides is routine and well-known in the art.

Thus, the invention of claims 1-15, 17-21, 24, 25 and 27 would have been obvious, as a whole, at the time the invention was made.

### ***Response to Arguments***

The rejection over the combination of John et al. and Fosnaugh et al. is withdrawn in the interests of simplifying prosecution.

Applicants traverse the remaining obviousness rejection by arguing the cited references fail to suggest the claimed oligonucleotide.

With regard to the Bass reference, applicants state that it is not the case that Bass teaches that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense technique by working more often and further argues that Bass does not disclose routine use of siRNA in mammalian cells.

Applicants appear to be misunderstanding the teachings of Bass as they relate to the rejection of record. Bass is not relied upon to teach routine use of siRNA in mammalian cells and the rejection does not state this; the rejection states that RNA interference is a known technique with several advantages over antisense. Bass teaches on page 429, first column (emphasis added) "... RNAi has repeatedly proven itself to be more robust than antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. And, as Tuschl and colleagues show, even in mammalian cells, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments."

With regard to Fosnaugh et al., applicants argue that Fosnaugh et al. do not provide a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene because this reference discloses only a series of vague and theoretical

considerations to make siRNAs and is based mainly on the blind screening of thousands of siRNAs. Applicants further argue the reference does not illustrate any experimental data showing that inhibitory siRNAs to the target gene were made.

These arguments are not persuasive because Fosnaugh et al. is not relied upon for a teaching of assays to screen thousands of siRNAs, but for the teachings cited in the rejection, specifically the structural elements of modified siRNAs, vectors, overhangs, etc.

Applicants further argue that Fosnaugh et al. is totally silent about the specificity of the siRNAs and because the siRNAs of Fosnaugh et al. are generated blindly they will include non-specific siRNAs targeting non-specific RNA targets.

This argument is not persuasive because the claims do not require the claimed siRNAs be specific for only one target and, as previously noted, Fosnaugh et al. is not relied upon for teaching a method of generating siRNAs.

Applicants argue that there is no motivation to make siRNA sequences targeting the regions disclosed in Wyatt et al., asserting that it is well known in the art that antisense oligonucleotides and siRNAs don't have the same targets. Applicants further argue that even if a motivation existed, one would have chosen other targets that, like the claimed siRNAs, show at least 80% inhibition.

The assertion that those in the art know that antisense and siRNAs do not have the same targets is not understood; it is unclear what applicants mean by "the same target" and the examiner does not understand how an antisense targeted to human casein kinase 2 and an siRNA targeted to this same gene would not have the same



target. The argument regarding whether one would have chosen the sequence of Wyatt et al. relied upon in the rejection is unpersuasive because the fact that one might also have reason make siRNAs targeted to other regions does not negate the teaching in Wyatt of SEQ ID NO: 60. No motivation to make a sequence that is 80% inhibitory is necessary because the claims do not require any level of inhibition.

Applicants argue the person having ordinary skill in the art could not arrive at the claimed invention by combining the teachings of Wyatt et al. and Fosnaugh et al. because making and testing a multitude of oligonucleotides targeted throughout the gene sequence is a theoretical solution which cannot be tested since it goes beyond the normal working capacity of the person having ordinary skill in the art.

This argument is unpersuasive because the rejection is not based on the making and testing of a large number of oligonucleotides, to arrive at the claimed invention requires only that one make the antisense of Wyatt et al. into an siRNA. At the time of filing those of ordinary skill in the art knew based on the teachings of Fosnaugh et al. that siRNAs are duplex RNAs generally 19-25 nucleotides in length that comprise a sequence identical to the target gene and a sequence complementary to the target (see paragraphs 13 and 33).

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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